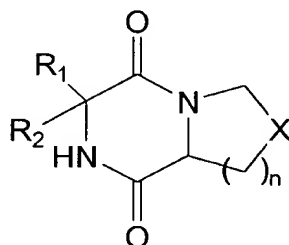


## Exhibit A

12. (Once Amended) A method of providing neuroprotection, said method comprising the step of administering to a subject an effective amount of a compound having the formula:



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

n is an integer from 0 to 3;

X is selected from the group consisting of -S-, -O-, -NR- and -CH<sub>2</sub>-;

R<sub>1</sub> and R<sub>2</sub> are each independently selected from the group consisting of -H, -OR, -SR, -NRR, -NO<sub>2</sub>, -CN, -C(O)OR, -C(O)NRR, -C(NR)NRR, trihalomethyl, halogen, (C<sub>1</sub>-C<sub>6</sub>) alkyl, substituted (C<sub>1</sub>-C<sub>6</sub>) alkyl, (C<sub>2</sub>-C<sub>6</sub>) alkenyl, substituted (C<sub>2</sub>-C<sub>6</sub>) (C<sub>2</sub>-C<sub>6</sub>) alkenyl, (C<sub>2</sub>-C<sub>6</sub>) alkynyl, substituted (C<sub>2</sub>-C<sub>6</sub>) alkynyl, (C<sub>5</sub>-C<sub>20</sub>) aryl, substituted (C<sub>5</sub>-C<sub>20</sub>) aryl, 5-20 membered heteroaryl, substituted 5-20 membered heteroaryl, (C<sub>6</sub>-C<sub>26</sub>) alkaryl, substituted (C<sub>6</sub>-C<sub>26</sub>) alkaryl, 6-26 membered alk-heteroaryl and substituted 6-26 membered alk-heteroaryl, or R<sub>1</sub> and R<sub>2</sub> taken together are -CH<sub>2</sub>-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>2</sub>-, where m is an integer from 0 to 6;

each alkyl, alkenyl, alkynyl, aryl, alkaryl, heteroaryl or alk-heteroaryl substituent is independently selected from the group consisting of -OR, -SR, -NRR, -CN, -NO<sub>2</sub>, -C(O)OR, -C(O)NRR, -C(S)NRR, -C(NR)NRR, halogen and trihalomethyl; and

each R is independently selected from the group consisting of -H, (C<sub>1</sub>-C<sub>6</sub>) alkyl, (C<sub>2</sub>-C<sub>6</sub>) alkenyl, (C<sub>2</sub>-C<sub>6</sub>) alkynyl, (C<sub>5</sub>-C<sub>20</sub>) aryl, 5-20 membered heteroaryl, (C<sub>6</sub>-C<sub>26</sub>) alkaryl and 6-26 membered alk-heteroaryl.

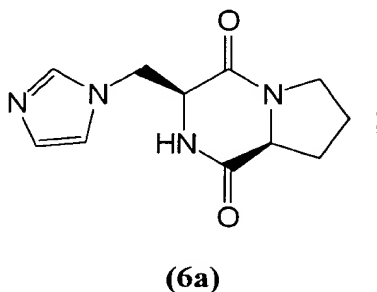
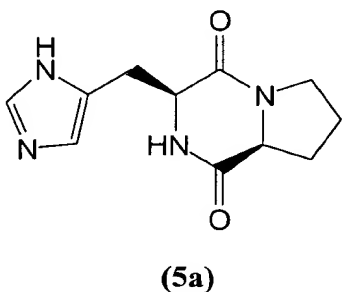
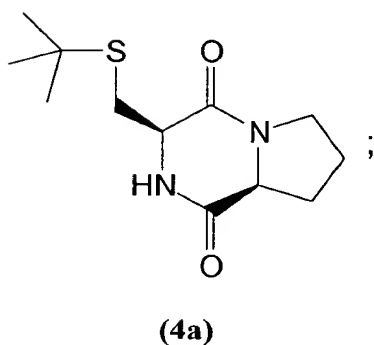
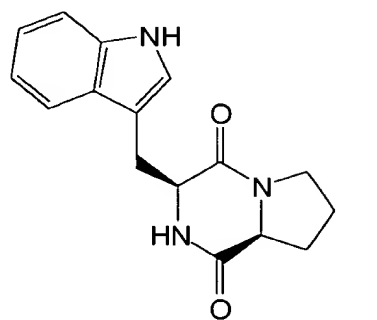
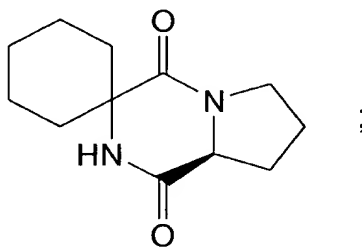
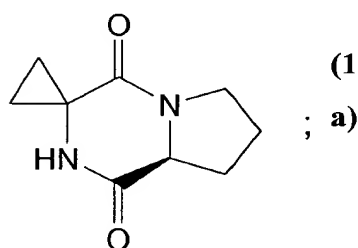
13. (Once Amended) The method of Claim 12, wherein the subject has a neurological disorder, a neurodegenerative disease or a CNS injury.

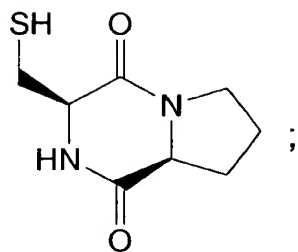
14. The method of Claim 12, wherein both carbons at positions 3 and 6 of the parent bicyclic 2,5-diketopiperazine ring are in the S configuration.

15. The method of Claim 12, wherein X is  $-\text{CH}_2-$ .

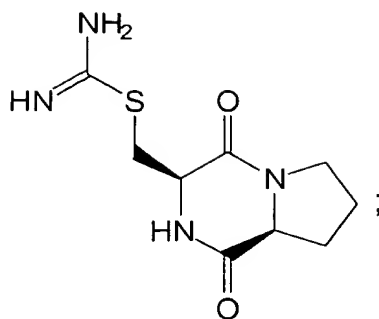
16. The method of Claim 12, wherein n is 1.

17. The method of Claim 12, wherein said compound is selected from the group consisting of:

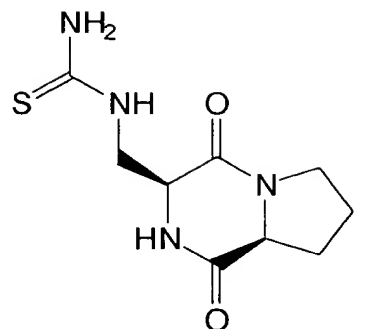




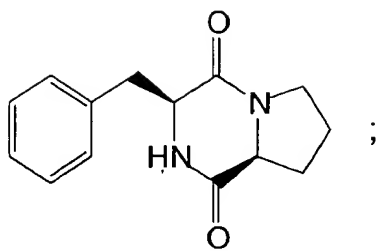
(7a)



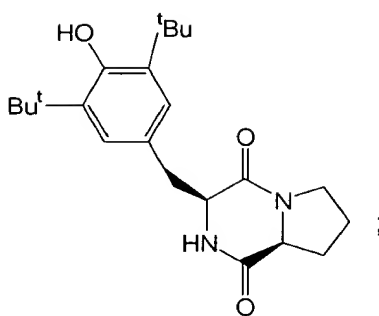
(8a)



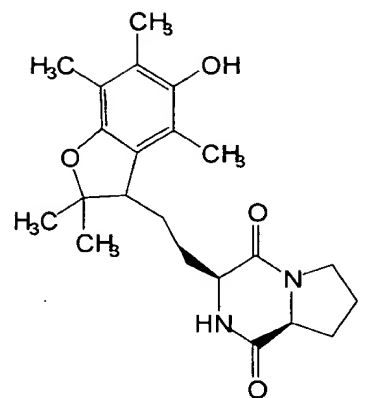
(9a)



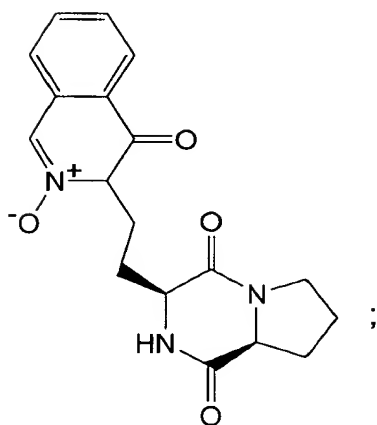
(10a)



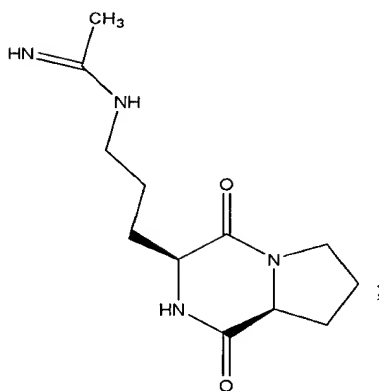
(11a)



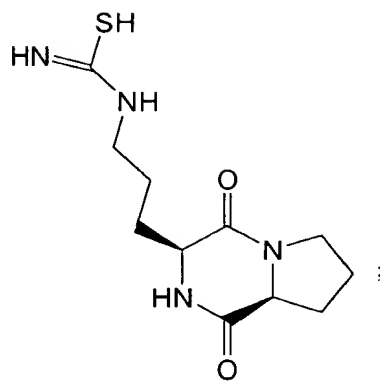
(12a)



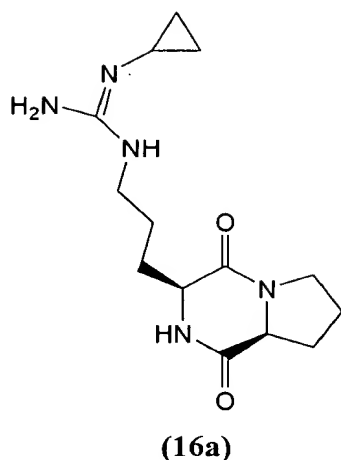
(13a)



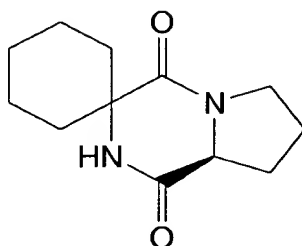
(14a)



(15a)

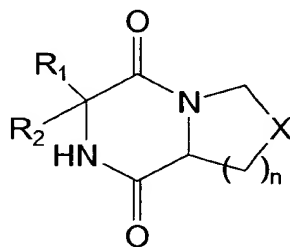


21. The method of Claim 12 in which said compound has the following structure:



22. (Once Amended) The method of Claim 13 in which the neurological disorder is caused by brain or spinal cord trauma.

23. A method of enhancing cognitive function, said method comprising the step of administering to a subject an effective amount of a compound having the formula:



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

$n$  is an integer from 0 to 3;

$X$  is selected from the group consisting of  $-S-$ ,  $-O-$ ,  $-NR-$  and  $-CH_2-$ ;

$R_1$  and  $R_2$  are each independently selected from the group consisting of -H, -OR, -SR, -NRR, -NO<sub>2</sub>, -CN, -C(O)OR, -C(O)NRR, -C(NR)NRR, trihalomethyl, halogen, (C<sub>1</sub>-C<sub>6</sub>) alkyl, substituted (C<sub>1</sub>-C<sub>6</sub>) alkyl, (C<sub>2</sub>-C<sub>6</sub>) alkenyl, substituted (C<sub>2</sub>-C<sub>6</sub>) alkenyl, (C<sub>2</sub>-C<sub>6</sub>) alkynyl, substituted (C<sub>2</sub>-C<sub>6</sub>) alkynyl, (C<sub>5</sub>-C<sub>20</sub>) aryl, substituted (C<sub>5</sub>-C<sub>20</sub>) aryl, 5-20 membered heteroaryl, substituted 5-20 membered heteroaryl, (C<sub>6</sub>-C<sub>26</sub>) alkaryl, substituted (C<sub>6</sub>-C<sub>26</sub>) alkaryl, 6-26 membered alk-heteroaryl and substituted 6-26 membered alk-heteroaryl, or  $R_1$  and  $R_2$  taken together are -CH<sub>2</sub>-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>2</sub>-, where m is an integer from 0 to 6;

each alkyl, alkenyl, alkynyl, aryl, alkaryl, heteroaryl or alk-heteroaryl substituent is independently selected from the group consisting of -OR, -SR, -NRR, -CN, -NO<sub>2</sub>, -C(O)OR, -C(O)NRR, -C(S)NRR, -C(NR)NRR, halogen and trihalomethyl; and

each R is independently selected from the group consisting of -H, (C<sub>1</sub>-C<sub>6</sub>) alkyl, (C<sub>2</sub>-C<sub>6</sub>) alkenyl, (C<sub>2</sub>-C<sub>6</sub>) alkynyl, (C<sub>5</sub>-C<sub>20</sub>) aryl, 5-20 membered heteroaryl, (C<sub>6</sub>-C<sub>26</sub>) alkaryl and 6-26 membered alk-heteroaryl.

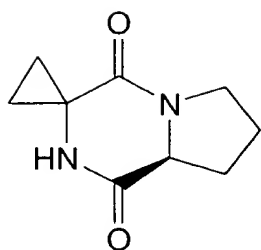
24. The method of Claim 23, wherein the cognitive function is memory.

25. The method of Claim 23, wherein both carbons at positions 3 and 6 of the parent bicyclic 2,5-diketopiperazine ring are in the S configuration.

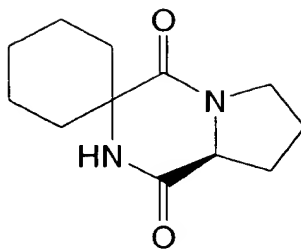
26. The method of Claim 23, wherein X is -CH<sub>2</sub>-.

27. The method of Claim 23, wherein n is 1.

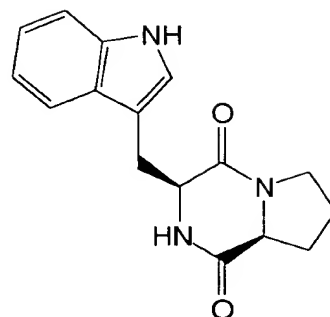
28. The method of Claim 23, wherein said compound is selected from the group consisting of:



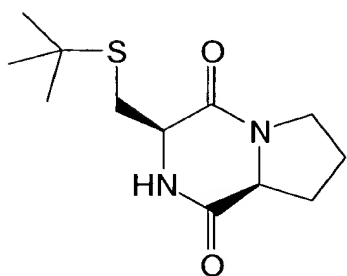
(1)  
; a)



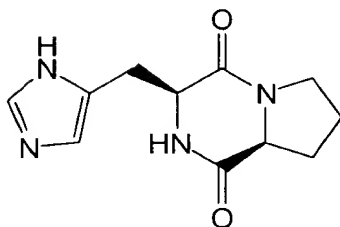
(2a)



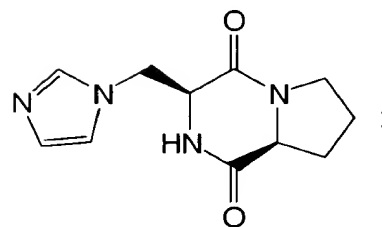
(3a)



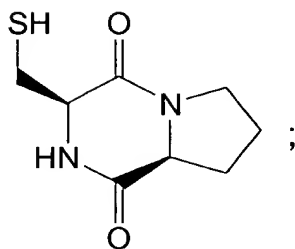
(4a)



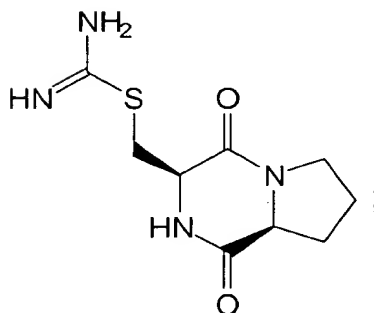
(5a)



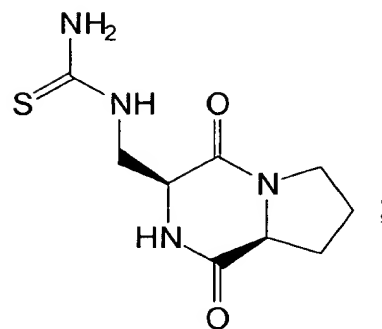
(6a)



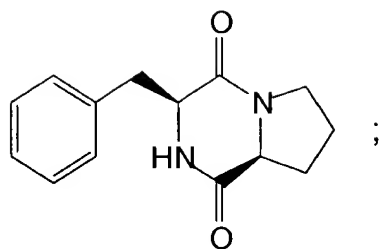
(7a)



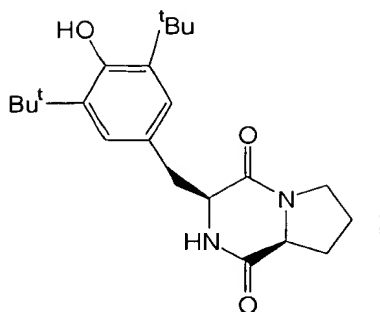
(8a)



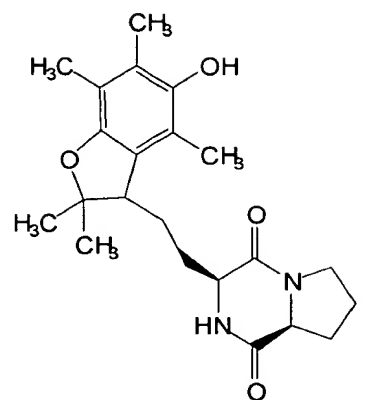
(9a)



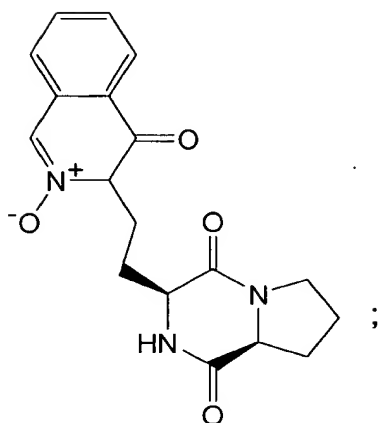
(10a)



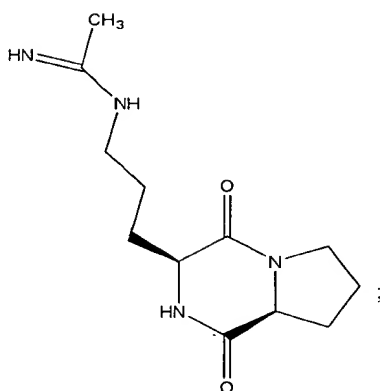
(11a)



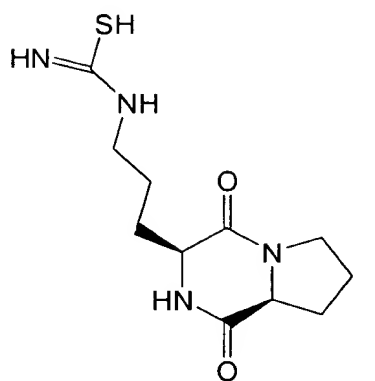
(12a)



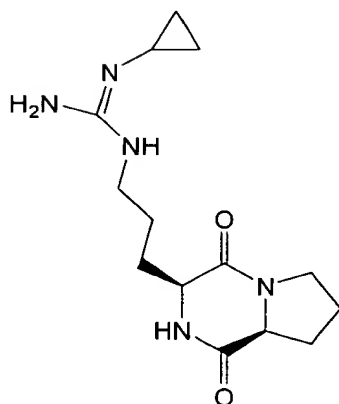
(13a)



(14a)

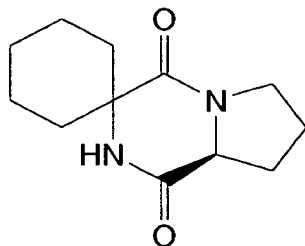


(15a)



(16a)

31. The method of Claim 23 in which said compound has the following structure:



32. The method of Claim 23, wherein said compound is administered following acute or chronic brain injury.

73. (New) The method of Claim 13 in which the CNS injury is caused by stroke.

74. (New) The method of Claim 12, wherein  $R_1$  is H.

75. (New) The method of Claim 74, wherein n is an integer from 1 to 3;

X is -S-, -O-, -NH- or -CH<sub>2</sub>-;

$R_2$  is -CH<sub>2</sub>- $R_5$ , -CH<sub>2</sub>-CH<sub>2</sub>- $R_5$  or -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>- $R_5$ ;

$R_5$  is phenyl, imidazolyl other than imidazol-2-yl, indolyl other than indol-3-yl, -SR<sub>6</sub>, -OR<sub>6</sub> or -NHR<sub>6</sub>; and

$R_6$  is -H, (C<sub>1</sub>-C<sub>6</sub>) alkyl (preferably t-butyl), (C<sub>2</sub>-C<sub>6</sub>) alkenyl, (C<sub>2</sub>-C<sub>6</sub>) alkynyl, -C(NH)NH<sub>2</sub> or -C(S)NH<sub>2</sub>.

76. (New) The method of Claim 74, wherein n is an integer from 1 to 3;

X is -S-, -O-, -NH- or -CH<sub>2</sub>-;

$R_2$  is -H, (C<sub>1</sub>-C<sub>6</sub>) alkyl, (C<sub>2</sub>-C<sub>6</sub>) alkenyl, (C<sub>2</sub>-C<sub>6</sub>) alkynyl or -(CH<sub>2</sub>)<sub>g</sub>-CH<sub>2</sub>- $R_7$ ;

g is an integer from 0 to 5;

$R_7$  is -OR<sub>8</sub>, -SR<sub>8</sub>, -NR<sub>8</sub>R<sub>8</sub>, -CH(OR<sub>8</sub>)-CH<sub>3</sub>, -C(O)R<sub>8</sub>, -C(O)OR<sub>8</sub>, -C(O)NR<sub>8</sub>R<sub>8</sub>, -S-C(NH)NH<sub>2</sub>, -NH-C(NH)NH<sub>2</sub>, -NH-C(S)NH<sub>2</sub>, phenyl, hydroxyphenyl, imidazolyl, indolyl; and

$R_8$  is -H, (C<sub>1</sub>-C<sub>6</sub>) alkyl, (C<sub>2</sub>-C<sub>6</sub>) alkenyl, (C<sub>2</sub>-C<sub>6</sub>) alkynyl.



77. (New) The method of Claim 74, wherein n is an integer from 1 to 3;  
 X is -S-, -O-, -NH- or -CH<sub>2</sub>-; and  
 R<sub>1</sub> and R<sub>2</sub> taken together are -CH<sub>2</sub>-(CH<sub>2</sub>)<sub>b</sub>-CH<sub>2</sub>-, where b is an integer from 0 to 6.
78. (New) The method of Claim 23, wherein R<sub>1</sub> is H.
79. (New) The method of Claim 78, wherein n is an integer from 1 to 3;  
 X is -S-, -O-, -NH- or -CH<sub>2</sub>-;  
 R<sub>2</sub> is -CH<sub>2</sub>-R<sub>5</sub>, -CH<sub>2</sub>-CH<sub>2</sub>-R<sub>5</sub> or -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-R<sub>5</sub>;  
 R<sub>5</sub> is phenyl, imidazolyl other than imidazol-2-yl, indolyl other than indol-3-yl, -SR<sub>6</sub>, -OR<sub>6</sub> or -NHR<sub>6</sub>; and  
 R<sub>6</sub> is -H, (C<sub>1</sub>-C<sub>6</sub>) alkyl (preferably t-butyl), (C<sub>2</sub>-C<sub>6</sub>) alkenyl, (C<sub>2</sub>-C<sub>6</sub>) alkynyl, -C(NH)NH<sub>2</sub> or -C(S)NH<sub>2</sub>.
80. (New) The method of Claim 78, wherein n is an integer from 1 to 3;  
 X is -S-, -O-, -NH- or -CH<sub>2</sub>-;  
 R<sub>2</sub> is -H, (C<sub>1</sub>-C<sub>6</sub>) alkyl, (C<sub>2</sub>-C<sub>6</sub>) alkenyl, (C<sub>2</sub>-C<sub>6</sub>) alkynyl or -(CH<sub>2</sub>)<sub>g</sub>-CH<sub>2</sub>-R<sub>7</sub>;  
 g is an integer from 0 to 5;  
 R<sub>7</sub> is -OR<sub>8</sub>, -SR<sub>8</sub>, -NR<sub>8</sub>R<sub>8</sub>, -CH(OR<sub>8</sub>)-CH<sub>3</sub>, -C(O)R<sub>8</sub>, -C(O)OR<sub>8</sub>, -C(O)NR<sub>8</sub>R<sub>8</sub>, -S-C(NH)NH<sub>2</sub>, -NH-C(NH)NH<sub>2</sub>, -NH-C(S)NH<sub>2</sub>, phenyl, hydroxyphenyl, imidazolyl, indolyl;  
 and  
 R<sub>8</sub> is -H, (C<sub>1</sub>-C<sub>6</sub>) alkyl, (C<sub>2</sub>-C<sub>6</sub>) alkenyl, (C<sub>2</sub>-C<sub>6</sub>) alkynyl.
81. (New) The method of Claim 78, wherein n is an integer from 1 to 3;  
 X is -S-, -O-, -NH- or -CH<sub>2</sub>-; and  
 R<sub>1</sub> and R<sub>2</sub> taken together are -CH<sub>2</sub>-(CH<sub>2</sub>)<sub>b</sub>-CH<sub>2</sub>-, where b is an integer from 0 to 6.